Tetrahedron Letters 57 (2016) 1066–1070

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-free Sonogashira-type cross-coupling reaction of bromoisoxazolines or *N*-alkoxyimidoyl bromides and alkynes

N. P. Probst, B. Deprez, N. Willand *

Univ. Lille, Inserm, Institut Pasteur de Lille, U1177—Drugs and Molecules for Living Systems, F-59000 Lille, France

ARTICLE INFO

Article history:
Received 17 December 2015
Revised 12 January 2016
Accepted 19 January 2016
Available online 21 January 2016

Keywords:
Sonogashira-type
Copper catalysis
Catalysis
Isoxazoline

ABSTRACT

A Cu(I)-catalysed Sonogashira-type cross coupling reaction with aliphatic or aromatic bromoisoxazolines or *N*-alkoxyimidoyl bromides and alkynes is reported. The protocol we developed employs catalytic amount of copper(I), non-toxic ligand bathophenanthroline and is tolerant to a wide range of functional groups and is therefore particulary adapted in the context of drug discovery.

Introduction

Palladium and copper co-catalysed Sonogashira-Hagihara cross-coupling reaction is widely used for the formation of sp^2–sp carbon–carbon bonds under mild conditions with aryl or vinyl halides (or triflate) and is frequently employed for the synthesis of biologically active molecules, heterocycles, natural products and in other chemical fields such as electronics or polymers.[1] Typical procedures involve the use of palladium phosphine complexes with CuI as the co-catalyst and large amounts of amines as the solvents or co-solvents.[2] To circumvent the high cost and relative higher toxicity of palladium compared to copper, catalytic systems without palladium have been successfully reported in the literature, combined with ligands such as phosphines,[3] nitrogen[4] and oxygen-containing molecules.[5] Even coupling reactions without the use of any transition metal have been published.[6]

Nevertheless, coupling partners such as acid chlorides and imidoyl halides have received less attention, with only few examples of catalytic coupling reaction between *N*-alkoxybenzimidoyl halides, and alkynes are described in the literature.[7] Those examples were restricted to aromatic groups attached to the sp^2 carbon and with the use of catalytic amount of palladium(II) complex (Scheme 1A).[8]

Here, we describe the first palladium-free cross-coupling reaction between bromoisoxazolines and alkynes in the presence of a catalytic amount of copper bromide and phenanthroline based-ligand (Scheme 1B). An extension to *N*-alkoxylalkylimidoyl bromides is also reported.

Results and discussion

At the outset of our investigations, we carried out the Sonogashira cross-coupling reaction between bromospiroisoxazoline **1a** and phenylacetylene **2a** under standard Sonogashira conditions.[9] Unfortunately, the desired cross-coupling product was not obtained, and a considerable amount of side products was observed.

Solvents were first screened (Table 1) with CuBr as a cheap copper(I) source. For the first time the desired product was observed with the combination of Na_2CO_3 and DMF. (HPLC yield: 4% yield with Bn_2O as the internal standard, Table 1, entry 1), whereas with toluene, THF or 1,4-dioxane as solvents no desired coupled product was detected, suggesting a dissociative pathway.

To reduce the catalytic charge of copper (in our first experiment loaded at 50 mol %) while trying to increase significantly the yield, we investigated different ligands, bases, copper sources (Table 2). At 100 °C, only ligands **L1** and **L8** containing aromatic nitrogen as donor groups (Table 2, entries 1 and 5) yielded the desired compound **3aa** with more than 10% HPLC yield, compared to those bearing secondary and tertiary amines (Table 2, entries 2–4).

At higher temperature (120 °C), phenanthroline **L1** and 2,2′-bipyridyl **L8** (Table 2, entries 6 and 7) associated with CuBr were

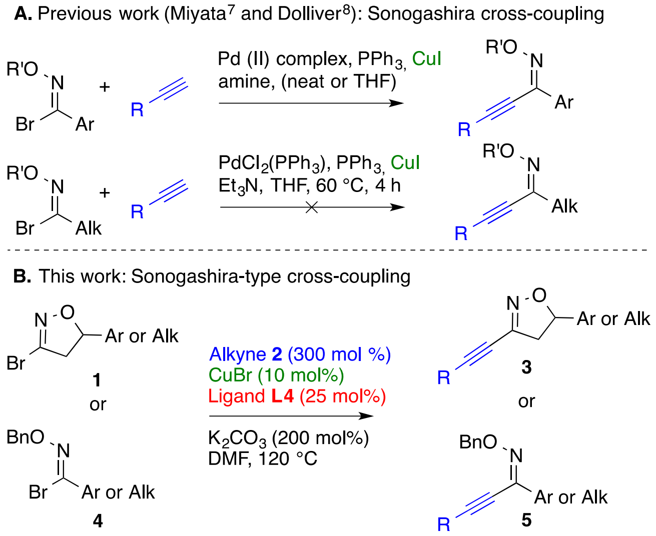
---

* Corresponding author at present address: Faculté de Pharmacie, 3 rue du Professeur Laguesse, 59000 Lille, France. Tel.: +33 3 20 96 49 91; fax: +33 3 20 96 47 09.

E-mail address: nicolas.willand@univ-lille2.fr (N. Willand).

URL: http://www.deprezlab.fr (N. Willand).

http://dx.doi.org/10.1016/j.tetlet.2016.01.070



Scheme 1.

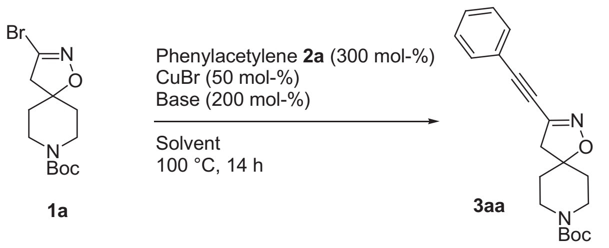
able to catalyse the reaction, affording respectively 61% and 40% HPLC yield. At 140 °C (Table 2, entry 8) the formation of the desired compound was not improved. The use of K_2CO_3 afforded a significant better yield (Table 2, entry 9). When phenanthroline based-ligands (**L1** to **L4**) were used, we were allowed to halve the catalytic loadings of CuBr and ligands respectively to 10 and 25 mol %. 4,7-dihydroxy-1,10-phenanthroline **L2** (Table 2, entry 10) failed to catalyse the reaction while neocuproin **L3** (Table 2, entry 11) was less effective than phenanthroline **L1** (Table 2, entry 12). Interestingly, the reaction was as efficient with CuI (Table 2, entry 13) and CuBr (Table 2, entry 12) as copper sources, whereas CuCl (Table 2, entry 14) was less efficient for this transformation. When the reaction was carried out at 120 °C using 25 mol % of bathophenanthroline **L4** (Table 2, entry 15), 200 mol % of K_2CO_3 and 10 mol % of CuBr, a quantitative HPLC yield was obtained and the desired compound was isolated with a 84% yield after flash chromatography. The copper free reaction (entry 16) did not lead to any formation of the cross-coupling product, excluding a competitive addition-elimination reaction pathway catalysed by the phenanthroline alone.

Next, we explored the scope of this reaction starting with substituted terminal alkynes. Electron rich (4-methoxyphenylacetylene **2c**) and electron poor aromatic alkynes (4-fluorophenylacetylene **2b** and 2-ethynylpyridine **2e**) afforded the coupling products in excellent yields but no conversion was observed with 1-ethynyl-4-nitrobenzene (**2d**). Interestingly 2-ethynylpyridine **2e** showed a remarkable reactivity, affording complete consumption of the starting bromoisoxazoline **1a** within 3 h.

The phenylacetylene derivatives (**2a** to **2e**) afforded in general better yields compared to aliphatic or functionalized alkynes **2f** to **2i**. Aliphatic alkynes **2g** and **2h** also afforded the targeted compounds in good yields however to overcome the Castro-Stephens homocoupling reaction, ten equivalents of cyclohexylacetylene **2f** and cyclopropylacetylene **2i** were used for the synthesis of the corresponding isoxazolines **3af** and **3ai**. To broaden the scope of the reaction, we performed the reaction with bromoisoxazolines bearing an ester (**1b** and **1c**), a free alcohol (**1e**) or a *tert*-butylcarbamate group (**1f**) and we also succeeded in isolating the desired compounds in good yields. The *cis*-fused ring isoxazoline **3da** was also easily obtained following the same protocol (Table 3).

Table 1

Solvent optimization of the Sonogashira-type cross-coupling reaction with bromoisoxazoline **1a** and phenylacetylene **2a**[a]



Entry	Base	Solvent	Yield[b] (%)
1	Na_2CO_3	DMF	4
2	Na_2CO_3	THF	nr[c]
3	Na_2CO_3	Toluene	nr[c]
4	Na_2CO_3	1,4-Dioxane	nr[c]

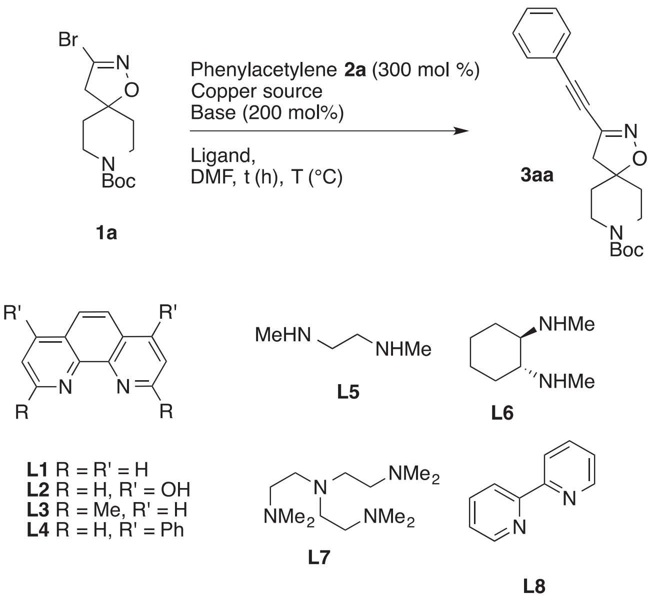
[a] Conditions: bromoisoxazoline **1a** (0.157 mmol, 100 mol %), phenylacetylene **2a** (300 mol %), base (200 mol %), CuBr (50 mol %) in DMF (1.5 mL) at 100 °C for 14 h.

[b] HPLC yield of **3aa** relative to Bn_2O as the internal standard.

[c] No reaction.

Table 2

Ligand optimization of the Sonogashira-type cross-coupling reaction with bromoisoxazoline **1a** and phenylacetylene **2a**[a]



Entry	Base	Cu source (mol %)	Ligand (mol %)	Time (h)	Temp. (°C)	Yield[b]
1	Na_2CO_3	CuBr (20)	**L1** (50)	14	100	16
2	Na_2CO_3	CuBr (20)	**L5** (50)	14	100	8
3	Na_2CO_3	CuBr (20)	**L6** (50)	14	100	9
4	Na_2CO_3	CuBr (20)	**L7** (50)	14	100	5
5	Na_2CO_3	CuBr (20)	**L8** (50)	14	100	15
6	Na_2CO_3	CuBr (20)	**L1** (50)	20	120	61
7	Na_2CO_3	CuBr (20)	**L8** (50)	20	120	40
8	Na_2CO_3	CuBr (20)	**L1** (50)	20	140	65
9	K_2CO_3	CuBr (20)	**L1** (50)	3	120	84
10	K_2CO_3	CuBr (10)	**L2** (25)	9	120	nr[c]
11	K_2CO_3	CuBr (10)	**L3** (25)	9	120	20
12	K_2CO_3	CuBr (10)	**L1** (25)	9	120	73
13	K_2CO_3	CuI (10)	**L1** (25)	9	120	72
14	K_2CO_3	CuCl (10)	**L1** (25)	9	120	57
15	K_2CO_3	CuBr (10)	**L4** (25)	9	120	91 (84[d])
16	K_2CO_3	—	**L1** (50)	20	120	nr[c]

[a] Conditions: bromoisoxazoline **1a** (0.157 mmol, 100 mol %), phenylacetylene **2a** (300 mol %), base (200 mol %), copper source, ligand, DMF (1.5 mL).

[b] HPLC yield of **3aa** relative to Bn_2O as the internal standard.

[c] No reaction.

[d] Isolated yield after flash chromatography.